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National Cancer

Institute

MELANOMA

RESEARCH REPORT

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This publication describes current research on incidence, possible causes, prevention, detection, diagnosis, and treatment of melanoma. When this tumor develops in the skin, it is called melanoma, or malignant melanoma. When it affects the eye, it is called ocular melanoma. These two cancers are discussed separately.

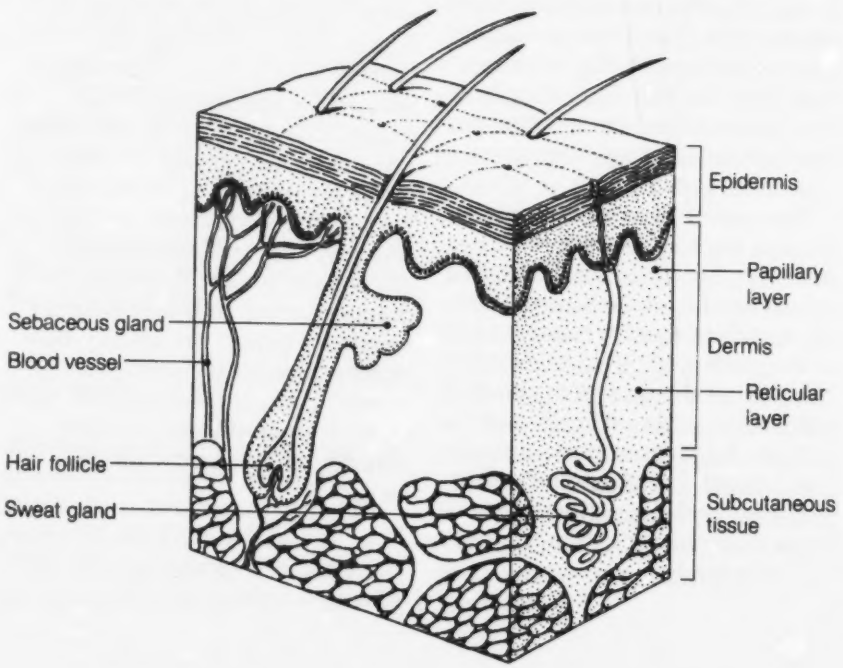
This information was gathered from medical textbooks, recent articles in the medical literature, and discussions with researchers at the National Cancer Institute (NCI) and other scientists. This Report expands upon the NCI pamphlet called *What You Need To Know About Melanoma.*

Knowledge about melanoma is increasing steadily. The most up-to-date information on this and other cancer-related subjects is available from the toll-free Cancer Information Service at 1-800-4-CANCER.

Cutaneous Melanoma

Description and Function of the Skin

As the body's outer covering, the skin offers protection from extreme temperatures, light, injury, infection, and many chemicals. The largest organ of the body, the skin



also regulates body temperature, stores water and fat, and helps to make vitamin D. By sending information to the brain about temperature, pressure, vibration, pain, and touch, the skin also senses the environment.

The skin has two main layers—the inner dermis and the outer epidermis. The dermis, in turn, is divided into an upper part called the papillary dermis and a lower portion named the recticular dermis. The dermis contains cells, fibrous tissue, blood and lymph vessels, sweat and sebaceous glands, and the follicles (hair shafts) through which hair grows. Blood vessels in the dermis supply the skin with nutrients. When sweat evaporates, it cools the skin and regulates body temperature. The sebaceous glands produce sebum, an oily substance that keeps the skin from drying out. Sweat and sebum reach the skin's surface through tiny openings called pores.

The epidermis, the outermost layer of the skin, is made up mostly of flat, scalelike cells called squamous cells. Less common are the round basal cells, found mainly in the lower part of the epidermis. This part of the epidermis also contains melanocytes, the cells that produce the pigment called melanin. The amount of melanin in the skin accounts for the variations in skin color found among different races and individuals.

Types of Skin Cancer

Skin cell growth begins at the base of the epidermis. New cells push older cells to the skin's surface, where they eventually die and flake off. In this way, the skin constantly repairs itself as new cells grow and multiply in an orderly way to replace dying ones.

Sometimes, though, cell growth becomes disordered, abnormal growth takes place, and a mass of tissue known as a tumor develops. Tumors can be either benign or malignant. Benign tumors are not cancer. They do not spread to other parts of the body and generally do not threaten life. Benign growths can usually be removed and seldom return. Malignant tumors are cancerous. They can invade and destroy healthy tissue and extend into nearby healthy tissues and organs. Cancer cells can also break away from the original (primary) tumor and spread, or metastasize, through the bloodstream or lymphatic system to form metastatic (secondary) tumors in distant organs. Cancer cells that make up secondary tumors are usually identical to those found in the primary cancer. Thus, although another part of the body is affected, the new tumor is still the same type of cancer.

Melanoma, the subject of this Research Report, is a serious type of cancer that develops in the melanocytes. This disease is diagnosed and treated differently from other (nonmelanoma) skin cancers. Melanoma spreads both by extension into neighboring tissues and to other parts of the body through the lymphatic system and bloodstream. Metastatic melanomas may involve any organ.

The two most common types of skin cancer are basal cell carcinoma, which arises in the basal cells, and squamous cell carcinoma, which begins in the squamous cells of the epidermis. These cancers are often diagnosed and treated in the same way and are almost always curable. They are discussed in *Research Report: Nonmelanoma Skin Cancers—Basal and Squamous Cell Carcinomas.* In addition to melanoma, other, much less common types of cancer that can affect the skin include Kaposi's sarcoma and cutaneous T-cell lymphoma (also called mycosis fungoides). These cancers are not discussed in this Research Report.

Incidence

Approximately 27,000 new cases of cutaneous melanoma and 5,800 deaths from this disease were estimated for the United States in 1988. The incidence of melanoma in this country has increased steadily over the past 40 years. The lifetime risk is now estimated to be about 0.8 percent. Whites develop melanoma much more frequently than blacks or Asians and, therefore, suffer many more deaths from the disease as well. In the United States, the annual incidence among whites approaches 10 per 100,000 individuals; in blacks, the rate is about 1 per 100,000.

Causes and Prevention

Causes

As with other forms of skin cancer, the development of cutaneous melanoma is related to exposure to ultraviolet (UV) radiation from the sun. UV radiation covers wavelengths between 0 and 400 nanometers (nm). The group of wavelengths between 290 and 330 nm, called UV-B, reaches the earth's surface and causes most of the sun damage to the skin. People who live close to the equator receive more direct sun and, if not protected by darker skin, are more susceptible to developing melanoma. For example, Australia, which receives a high level of UV-B radiation, has an annual incidence of more than 17 cases per 100,000 people—one of the highest rates in the world. In addition, the rate of new cases of melanoma in the southwestern United States is now equal to or greater than the rate in Australia.

The rising incidence of melanoma may be due, in part, to changes in lifestyle and leisure activities. More people are exposing themselves to intense sunlight. In addition, concern is increasing that the atmosphere's ozone layer, which protects us from UV-B radiation, is being depleted by manmade products called chlorofluorocarbons, such as Freon. These products serve as propellants in aerosol sprays and as cooling agents in refrigerators and air conditioners. As the ozone layer thins, more UV-B radiation reaches the earth, increasing the likelihood that more cases of melanoma will be seen in the next decade.

Melanoma usually occurs in different areas of the body in light-skinned women and men. It develops most often on the arms and lower legs in women and on the head and neck in men. These sites are commonly exposed to light. However, another common site for melanoma to occur in men is the trunk. Because this site is not normally exposed to light, the relationship between UV-B exposure and melanoma location is not as clear-cut as is the relationship of UV-B to the development of nonmelanoma skin cancers. It appears likely that other risk factors play a role in the development of melanoma.

There is evidence that certain types of moles known as dysplastic nevi may give rise to cutaneous melanomas. (Nevus is the medical term for mole.) These nevi, which are different from common moles, can be inherited (familial dysplastic nevi), or they may occur sporadically in people who have no family history of dysplastic nevi.

Individuals with dysplastic nevi should be monitored by a doctor to detect and remove abnormal moles that are likely to lead to melanoma. Photographs of nevi are often helpful for followup examinations. Dysplastic nevi are generally larger than ordinary moles and have irregular borders that fade into the surrounding skin. They may be flat or raised above the skin surface. Their color—usually not uniform—may be dark brown, sometimes with pink or red areas. While the average adult has 10 to 40 moles, persons with dysplastic nevi often have more than 100 unusual moles on their skin. More information about this condition is given in the NCI publication titled *About Dysplastic Nevi.*

People with dysplastic nevi may have an increased risk of developing melanoma during their lifetime. Melanoma usually develops in the dysplastic nevi but may also develop in normal skin. The risk of developing melanoma is increased more than a hundredfold for persons with dysplastic nevi who are also from melanoma-prone families (i.e., people with two or more first-degree relatives—parents, children, brothers, sisters—with melanoma). Adult family members who do not have dysplastic nevi appear to have a nearly normal risk of developing melanoma.

Melanoma is also related to other noncancerous conditions. People who sunburn easily and tan poorly or who have blue eyes, red hair, or many moles have a greater risk of developing melanoma than do people who do not have these characteristics. Individuals with very large moles (20 centimeters, or 7.8 inches, in diameter) that are present from birth have a 5 to 20 percent risk of developing melanoma. Also, people with xeroderma pigmentosum, a rare hereditary disease in which the skin and eyes are extremely sensitive to light, are 1,000 times more likely to develop melanoma than the general population.

Prevention

Reducing sun exposure is one of the easiest ways to decrease the risk of developing melanoma, particularly for those individuals in sun-sensitive high-risk groups. Ultraviolet radiation exposure can be reduced 50 percent by avoiding the sun between 11 a.m. and 1 p.m. (12 p.m. and 2 p.m., daylight saving time). During spring and summer months, exposure to sunlight should be gradual. During winter vacations to tropical areas, intense exposure to the sun should be limited. Wearing protective clothing (such as hats and long sleeves) and using an effective sunscreen are also important. Sunscreens that block UV radiation usually contain para-aminobenzoic acid (PABA) or related compounds; they are rated in strength from 2 to 15 or higher. This sun protection factor (SPF) must be printed on the container. The higher the SPF rating, the greater the blockage of UV radiation.

To prevent melanoma, a person with dysplastic nevi is best advised to avoid excessive sunlight and have changing moles (as described on pages 6–7) surgically removed. Dysplastic nevi on the scalp should be removed because it is difficult to see changes in growths covered by hair. Individuals with dysplastic nevi from families with multiple cases of melanoma should be examined on a regular basis.

Detection and Diagnosis

Melanoma can begin in an existing mole or as a new, mole-like growth. If detected early, it can be effectively treated and cured. The first warning signs of melanoma should be promptly brought to the attention of a physician:

- *Large size.* If there is an increase (gradual or sudden) in the size of a mole, it may be a melanoma. Melanomas generally are at least 5 millimeters (mm) across (about ¼ inch).
- *Multiple colors.* Melanomas tend to have a variety of colors—red, white, blue, and sometimes black or dark brown—within a single mole.
- *Irregular border.* Melanomas often have uneven or notched borders.
- *Abnormal surface.* A mole may be a melanoma if it is scaly, flaky, oozing, bleeding, or has an open sore that does not heal.
- *Unusual texture.* If a mole feels hard or lumpy, it may be a melanoma.
- *Abnormal skin around a mole.* If pigment, or color, from a mole has spread to surrounding skin or if nearby skin is red or swollen or has lost its pigmentation (becomes white or gray), a melanoma may be present.
- *Unusual sensation.* A mole may be a melanoma if it itches or is painful and tender.
- *Change in appearance of the skin.* Melanomas may develop as new pigmented spots in a skin area that had been normal.

While experienced physicians, especially dermatologists, can often identify a melanoma on sight, a biopsy is the only sure way to make a diagnosis. The biopsy—surgical removal of the mole—can usually be done using local anesthesia in a doctor's office. Suspicious-looking areas should never be burned off. By examining the tissue under a microscope, a pathologist can determine whether the growth is benign (a mole) or cancerous (a basal or squamous cell carcinoma or a melanoma).

Staging

Once melanoma has been diagnosed, other tests help determine the extent (stage) of the disease. Staging procedures generally include a thorough physical examination and various x-rays. The stage of the melanoma, which is an important factor in selecting treatment, is determined by the thickness of the growth, the depth of skin penetration, and whether the cancer has spread to nearby lymph nodes or distant parts of the body.

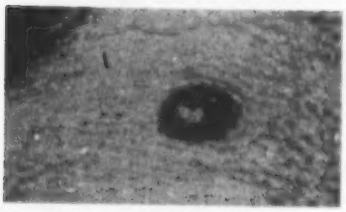
Remember the signs for early detection of melanoma. If you find anything unusual, see your doctor right away.

Photos courtesy of the Skin Cancer Foundation.

Normal Moles

Melanoma

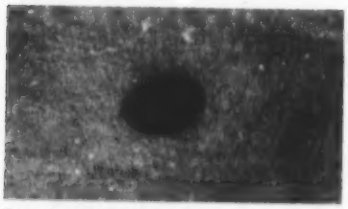
Shape



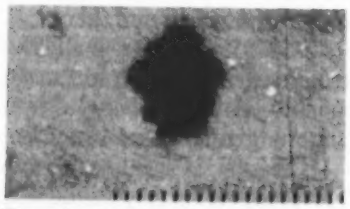
Round or oval with one half matching the other.

The shape of one half does not match the other.

Border

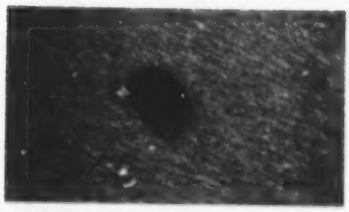


Clearly defined, smooth border.

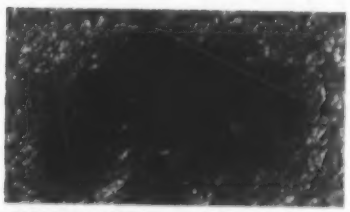


The edges are uneven, ragged, or notched.

Color



Uniformly tan or brown.



Different shades of brown, black or tan.

Diameter

Normal moles are usually less than 6 mm—the size of a pencil eraser.

Most melanomas are at least 5 mm in diameter. Any change in size.

Microstaging

Various researchers have studied the relationship between prognosis (outcome of the disease) and either the level of skin invaded or the thickness of the melanoma. Dr. Alexander Breslow, at the George Washington University, suggested measuring the thickness of the tumor. When he grouped melanomas by thickness, he found that the thicker the growth, the more likely that metastasis had occurred. He also found that survival ranged from almost 100 percent for patients with growths equal to or thinner than 0.75 mm, about 1/32 inch, to no greater than 20 percent for those with melanomas equal to or thicker than 4.0 mm (slightly greater than 1/8 inch).

Dr. Wallace Clark, Jr., at the University of Pennsylvania, found that a deeper level of invasion was associated with a poorer prognosis. Clark's classification system groups melanomas into five levels:

Level I: A cancer involving only the epidermis (the outer skin layer). Characterized by the abnormal growth of cells (atypical melanocytic hyperplasia), it is sometimes called melanoma *in situ* and may be regarded as nonmalignant.

Level II: Melanoma reaches into the papillary dermis (upper portion of the dermis).

Level III: Cancer extends to the bottom of the papillary dermis.

Level IV: Melanoma invades the reticular dermis (lower part of the dermis).

Level V: Cancer penetrates through the layers of the skin into the underlying tissue.

Stage of the Disease

The American Joint Committee on Cancer has developed a staging system based on coded descriptions of tumor size (T), lymph node involvement (N), and degree of metastasis (M). The amount of skin invasion determines the extent of the primary tumor. Cutaneous melanoma is classified TX when there is no evidence of primary tumor or this factor has not been or cannot be assessed; T0 when there is abnormal, but not cancerous, growth; or T with a number from 1 to 4, depending on the degree of skin invasion. Lymph nodes are

classified NX if they cannot be assessed; N0 if no cancer cells are found in the node(s); or N with the number 1 or 2, depending on the location of the node(s) containing cancer cells. Distant metastases are classified as MX when metastases cannot be assessed; M0 when no distant disease is found; M1 when distant metastases are present in the skin or tissues underneath it; or M2 when the disease affects distant organs.

The following staging system takes into account microstaging (Breslow's classification and Clark's levels) and the extent of spread to lymph nodes or distant organs.

Stage 0: Sometimes called *in situ;* Clark's level I.

Stage IA: Melanomas thinner than 0.75 mm (1/32 inch); Clark's level II. (T1, N0, M0)

Stage IB: Melanomas 0.76 mm to 1.5 mm (1/32 to 1/16 inch) in thickness; Clark's level III. (T2, N0, M0)

Stage IIA: Melanomas 1.51 mm to 4.0 mm (1/16 to 1/8 inch) in thickness; Clark's level IV. (T3, N0, M0)

Stage IIB: Melanomas 4.1 mm (1/8 inch) thick or greater; Clark's level V. (T4, N0, M0)

Stage III: Melanomas that have spread to only one group of nearby lymph nodes. (any T, N1, M0)

Stage IV: Melanomas that involve one enlarged and fixed lymph node group, more than one lymph node group, or another organ or area of skin. (any T, N2, M0; or any T, any N, M1 or M2)

Treatment

Treatment of melanomas that have not spread beyond the original area of growth (especially if they are thin and have not invaded the papillary dermis) is highly effective, and most of these cancers can be cured. Some melanomas that have spread to nearby lymph nodes also can be treated effectively. At present, however, current methods of therapy for melanomas that have spread to distant parts of the body are unsatisfactory, and many scientists are conducting basic research and clinical trials to find better forms of treatment. (Additional information about clinical trials is found on page 19.)

Surgery

About 95 percent of all patients with melanoma are treated with surgery. When the tumor is thin and has not spread beyond the initial area of growth (stage I), it is usually curable with surgery alone. Generally, the doctor removes the growth and a border of normal tissue around it to eliminate any cancer cells that may have spread from the tumor. Researchers have found that the removal of tissue surrounding the cancer is necessary to prevent recurrence. Wide excision, the removal of a large margin of tissue around a melanoma, is used to treat stage II and stage III disease. For this procedure, a skin graft may be necessary. At this time, a clinical trial is being conducted to determine whether wide excision is equivalent to or better than removing a smaller border of tissue during treatment for stage I melanoma.

This trial will also determine whether there is any benefit in taking out regional lymph nodes at the time a stage I melanoma is removed. Currently, lymph node removal is optional for treatment of stage I and stage II melanoma; removal may eliminate undetected cancer cells that have spread from the original cancer to the lymph nodes. Regional lymph nodes, or those affected by disease, are removed during a wide excision for stage III melanoma. For very advanced disease (stage IV), surgical removal of metastatic tumors and lymph nodes may help relieve symptoms and provide pain relief.

Chemotherapy

Patients with stage II and stage III melanoma face a high risk of disease recurrence. To improve the outlook for these patients, researchers are evaluating the use of chemotherapy to kill undetectable cancer cells that remain in the body after surgery (adjuvant chemotherapy). Drugs under investigation for the adjuvant treatment of stage II and stage III disease include carmustine (BCNU), cisplatin (Platinol), dacarbazine (DTIC), dactinomycin (Cosmegan), vinblastine (Velban), and vincristine (Oncovin).

An innovative method of administering chemotherapy is under investigation for patients with stage II or stage III melanoma in an arm or leg. Known as limb, or isolation, perfusion, this method enables

patients to receive high doses of anticancer drugs in the affected area so that side effects are not experienced throughout the body. This technique is based on the heart-lung machine developed in the early 1950's for heart surgery. In isolation perfusion, blood is withdrawn from the patient and pumped through a special machine that adds oxygen and the anticancer drugs. The blood is then pumped back into the major artery supplying the limb being treated. Often, the blood is heated to enhance the effects of the drugs. Drugs commonly used for perfusion are melphalan (Alkeran), mechlorethamine (Mustargen), and DTIC.

Because current methods of treatment for advanced melanoma are generally ineffective, researchers are looking for new anticancer drugs and combinations of drugs that may prove useful. Although many drugs and drug combinations have been evaluated, none has improved long-term survival for patients with widespread disease. Thus, clinical trials with chemotherapeutic agents are continuing, and patients with advanced disease should consider participating in these trials to evaluate new treatments. Drugs under investigation for stage IV or recurrent melanoma include vincristine, cisplatin, carmustine, and dacarbazine.

Biological Therapy

Biological therapy, also called immunotherapy, is another important area of research. Scientists have identified a number of naturally occurring and synthetic substances called biological response modifiers (BRMs), which can boost, direct, or restore the body's normal defenses (immune system). Clinical trials are exploring the potential of various types of biological therapy, both alone and in combination with other forms of treatment such as chemotherapy.

Researchers are studying the usefulness of certain BRMs in the adjuvant treatment of melanoma. One such BRM is interferon, a protein formed in small amounts by the body's cells; it can now be produced in the laboratory using recombinant interferon technology. Clinical trials are under way to determine whether the addition of recombinant interferon to initial surgical treatment will prevent recurrence of melanoma.

Studies are also under way to evaluate treatment of metastatic melanoma (stages III and IV) with recombinant interleukin-2 (IL-2),

a biological response modifier that activates the patient's white blood cells to form a unique type of killer cell. These cells, called lymphokine-activated killer (LAK) cells, destroy cancer cells. A patient may receive IL–2 alone or combined with LAK cells produced by treating the patient's white blood cells with IL–2. Thus far, results of studies with IL–2 and IL–2/LAK cell therapy have been promising. In other trials, monoclonal antibodies are combined with IL–2 or used alone for metastatic disease. Monoclonal antibodies are proteins produced in the laboratory. These special antibodies seek out specific cancer cells or parts of cancer cells; they can be bound to dyes, radioactive compounds, or poisons to locate and/or destroy the targeted cancer cells.

Radiation Therapy

Radiation therapy is of limited value in treating melanoma. However, in cases where the disease has spread (stage IV) to the lung, gastrointestinal tract, bone, or brain, radiation may provide relief from such symptoms as pain.

Recurrent Disease

Treatment for recurrent melanoma depends on prior therapy, the location and extent of recurrence, the patient's age and general health, and other factors. Investigational treatment, including chemotherapy and biological therapy, should be considered in patients with recurrent disease.

Followup Care

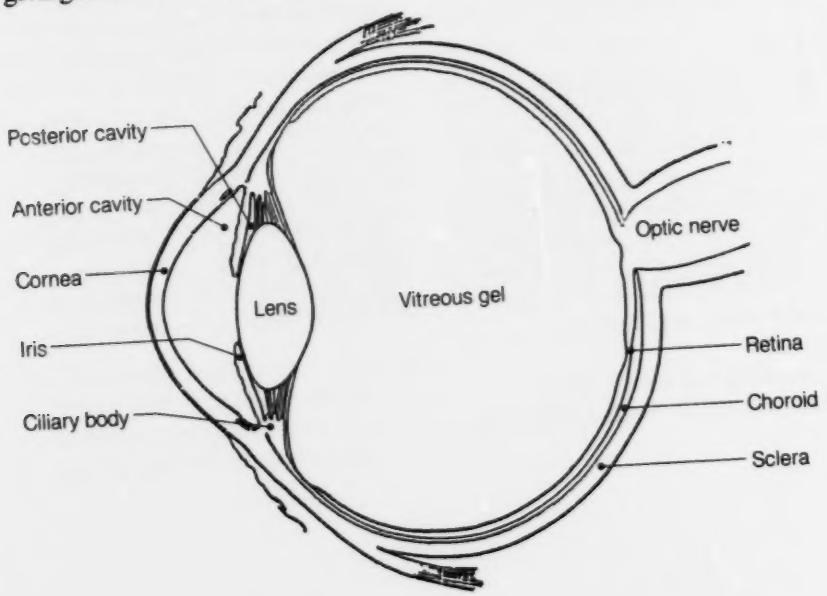
Because melanoma patients are at high risk for recurrence and for the development of new melanomas, they should be examined by a physician on a regular basis. Depending on the stage of the original growth, followup exams may include x-rays. Patients should also regularly examine their own skin.

Ocular Melanoma

Description and Function of the Eye

The eye is composed of three tissue regions and two inner cavities. The tissue regions are the outer group (the fibrous tunic) consisting of the sclera in the back of the eye and the cornea in the front; the middle group (the vascular tunic) consisting of the choroid, ciliary body, and the iris; and the inner retina, or nervous tunic. The anterior cavity located at the front of the eye and the posterior cavity at the back help give the eye its shape.

Sometimes, as described on page 2, normal pigmented cells grow in a disordered and abnormal way, giving rise to a cancerous tumor, or melanoma. Ocular melanoma develops in the pigmented vascular tunic. Also called the uvea, this area includes the iris, the ciliary body, and choroid. The iris is a circular group of muscles that contract or relax to control the amount of light entering the pupil. The ciliary body is located at the edges of the iris, to which it is attached. It contains a muscle that alters the shape of the lens, which sits behind the iris and focuses light. The lens also separates the two eye cavities. At the back of the eye, the ciliary body connects with the choroid layer. The choroid layer nourishes the layer above it, called the retina. Ocular melanoma may develop in any of these three structures (iris, ciliary body, or choroid).



Incidence and Causes of Ocular Melanoma

Although ocular melanoma is the most common primary eye cancer in white adults, it is still very rare, with fewer than 6 new cases in every million people diagnosed each year. This form of melanoma is even rarer in blacks and Asians.

The causes of ocular melanoma are not well understood. One study suggests that sunlight plays a role in the development of this disease. Another study on the relationship of sunlight to this form of melanoma is in progress. Based on animal studies, some scientists believe that viruses and certain chemicals may be involved in the formation of ocular melanoma.

Symptoms and Diagnosis

Symptoms

Signs of this disease depend on where in the eye the cancer develops. Melanoma that develops in the iris may produce a pigmented spot, often noticed by the patient. Other signs include distortion of the pupil, presence of new blood vessels, curling of the iris near the pupil, and cataract formation.

Choroidal and ciliary body melanomas often reach a large size before symptoms are observed. These may include loss or deterioration of vision and the presence of floating spots. Cataracts, secondary glaucoma, and inflammation also may occur. Tumors in the choroid and ciliary body may not produce any symptoms and are often diagnosed during a routine eye examination.

Diagnosis

Diagnostic procedures for ocular melanoma depend upon where the disease begins. Melanoma that starts in the iris is easy to detect by the presence of a changing spot that varies in color from velvety brown to translucent or pink. Several diagnostic procedures for this tumor include:

- *Slit lamp examination,* in which light is projected into the eye through a slit, allowing the doctor to use a microscope to study the inside of the eye, lens, iris, cornea, and the surface of the eye. Sometimes the doctor may take pictures at successive appointments to see whether the tumor is growing. This procedure is called serial slit lamp photography.

- *Gonioscopy,* a procedure in which the doctor examines the angle of the front portion of the eye with a slit lamp or another instrument called a gonioscope. An obstruction of this angle may signal the presence of glaucoma and possibly melanoma.
- *Ophthalmoscopy,* the visual examination of the eye's interior, in which the doctor uses drops to dilate the pupil and a special instrument called an ophthalmoscope to view the inner eye, including the retina. Fundus photography, or pictures taken using an ophthalmoscope, is helpful in locating and characterizing an ocular melanoma.

Diagnosis of melanomas that begin in the choroid and ciliary body (grayish to brown tumors) usually include the examination techniques mentioned above, in addition to several others:

- *Fluorescein angiography,* in which the eye's blood vessels, including those that supply a tumor, are highlighted with a dye. This procedure can help distinguish an ocular melanoma from other types of tumors that may begin in the eye.
- *Ultrasonography,* a procedure in which high-frequency sound waves are projected into the eye and the echoes converted by a computer into a picture showing the shape, location, and tissue characteristics of a tumor inside the eye.
- *Computed tomography* (CT), in which a computer is used to produce a detailed x-ray picture of a cross-section of the eye. This test helps the doctor determine whether the tumor extends to the back of the eye.

When a diagnosis of ocular melanoma is made, a patient undergoes a full medical examination, which may include blood tests, x-rays, and scans of different organs to determine if the cancer has spread to other parts of the body. In 1 to 3 percent of patients with ocular melanoma, metastases to other areas are detected at the time of initial diagnosis. When melanoma spreads outside the eye, it most often appears in the liver. It can also spread to the lungs and areas directly under the skin. Other sites are less common.

Classification and Staging

Melanomas are classified by where they begin in the eye (iris, ciliary body, or choroid) and by their size.

Small melanomas have a diameter of less than 10 mm (5/12 inch), medium-size melanomas are between 10 and 15 mm (5/12 to 5/8 inch), and large melanomas exceed 15 mm (over 5/8 inch) in diameter. In addition, ocular melanomas are classified by the microscopic appearance of the cells. Most melanomas of the iris and some melanomas in the choroid and ciliary body are made of spindle cells. Spindle cell tumors are less likely to metastasize than nonspindle cell types. More aggressive melanomas include those composed of several nonspindle cell types and tumors in which spindle cells are mixed with nonspindle types.

Treatment

When ocular melanoma is detected and treated at an early stage, it may be curable, and vision can be preserved in some cases. The selection of treatment depends, in part, on tumor size, location, site of origin (whether it began in the iris, ciliary body, or choroid), and growth rate. Other factors affecting the choice of treatment are the degree of tumor invasion into the eye cavity and spread to nearby tissues, the presence of distant metastases, the patient's age and general health, eyesight in the affected and unaffected eye, and the patient's preference.

Iris

Melanomas of the iris are generally smaller, slower growing, and less aggressive than melanomas in the choroid and ciliary body. A doctor may recommend only careful monitoring of a melanoma in the iris if it appears to grow slowly and doesn't interfere with vision. For faster-growing tumors, surgical removal of the tumor may be suggested. If the tumor has grown over a large portion of the iris, impaired vision, or is too large to be excised, the whole eye may be removed in a procedure called enucleation. On the rare occasions that the tumor spreads beyond the eye, exenteration (removal of the eye plus the surrounding tissues) may be necessary.

Choroid and Ciliary Body

Until fairly recently, enucleation was the usual treatment for choroidal and ciliary melanomas. However, patients with melanomas in these areas of the eye now have more treatment options. Patients may simply be observed by a doctor, especially if the tumor is small and

appears slow-growing or inactive. Alternatively, the doctor may decide to use external radiation to shrink or destroy the tumor.

A new study is under way to develop a standard treatment for choroidal melanomas. One portion of this Collaborative Ocular Melanoma Study (COMS), sponsored by the National Eye Institute, will determine whether radiation therapy is better than enucleation in treating medium-size tumors. Half the patients receive radiation and half undergo enucleation. Radiation is given in the form of a radioactive plaque, made by placing radioactive pellets in a plastic disc covered on one side with a gold plate. The disc is sewn to the eye over the tumor. Radiation is directed to the tumor, while the gold plate protects the rest of the eye and surrounding tissues. This study will compare the effectiveness of each treatment, the relative risk of developing distant metastases, and the long-term survival of patients.

The amount of radiation needed to destroy a large melanoma, whether given by plaque or by other means, is often so great that the eye itself is severely injured or destroyed. Therefore, enucleation (or exenteration in the case of extraocular tumor extension) is still the recommended treatment for large tumors of the ciliary body and choroid. It is not known, however, whether external radiation given to shrink a tumor prior to enucleation improves the effectiveness of surgery. To help answer this question, patients in the COMS study with large melanomas will undergo either external radiation followed by enucleation or enucleation alone.

Side effects accompany each form of treatment. After enucleation, the eye area may be temporarily painful. Serious problems following radiation therapy may include bleeding within the eye (hemorrhage), cataract formation, glaucoma, inflammation, and other conditions. For this reason, patients should discuss treatment options and possible side effects with their doctor before beginning treatment. Several doctors, including an ophthalmologist (eye specialist) and an oncologist (cancer specialist), may need to be consulted to develop the best treatment plan.

The NCI is supporting an investigational study comparing external radiation using charged helium particles with radioactive iodine radiation implants in the treatment of localized ocular melanoma. This

study will compare the effectiveness of each treatment, long-term effects of treatment on vision, the relative risk of developing distant metastases, and long-term patient survival.

Doctors are looking at several investigational techniques to treat certain patients with ocular melanoma. Small melanomas of the choroid and ciliary body may be removed by surgical resection, in which the tumor plus underlying tissue is removed. One experimental procedure that reduces the amount of radiation necessary for treatment combines external radiation with hyperthermia, a technique in which the tumor is heated. However, hyperthermia may result in complications, including pain, inflammation, retinal detachment, loss of vision, and blindness.

Photocoagulation is a procedure being studied in the treatment of small tumors. In this process, the blood vessels entering the tumor are heated by a light beam and destroyed, thereby depriving the tumor of nutrients. Photocoagulation may be used in combination with radiation to treat small (under 10 mm) and medium-size (10–15 mm) tumors. In addition, photodynamic therapy with hematoporphyrin derivative (HPD) may be useful in treating these melanomas. Photodynamic therapy uses an interaction between light and a substance that makes cells more sensitive to light (photosensitizing agent) to destroy tumor tissue. When injected into the body, the HPD travels to and enters the tumor cells, sensitizing them to light. The tumor is destroyed when a beam of light is then directed at it.

Rehabilitation and Followup

Treatment results, side effects, and evidence of metastatic disease may not appear for several months to years following the initial therapy. Therefore, it is important that patients have regular followup examinations. Patients may also undergo some type of reconstructive surgery after treatment. For a patient who undergoes enucleation, a silicone ball is sewn inside the eye socket; this implant usually heals within 4 to 8 weeks. The patient is then fitted with an artificial eye, or prosthesis, which fits over the front of the silicone ball. The artificial eye looks and moves much like a real eye. Patients should discuss this and other reconstructive options with their doctor prior to therapy.

Clinical Trials and Physician Data Query (PDQ)

To improve the outcome of treatment for melanoma, the NCI supports clinical studies at many hospitals throughout the United States. Patients who take part in this research make an important contribution to medical science and may have the first chance to benefit from improved treatment methods. Physicians are encouraged to inform their patients about the option of participating in such studies. To help patients and doctors learn about clinical trials, the NCI has developed PDQ (Physician Data Query), a computerized database designed to give doctors quick and easy access to:

- descriptions of current clinical trials that are accepting patients, including information about the objectives of the study, medical eligibility requirements, details of the treatment program, and the names and addresses of physicians and facilities conducting the study;
- the latest treatment information for most types of cancer; and
- names and addresses of physicians and organizations involved in cancer care.

To access PDQ, a doctor may use an office computer with a telephone hookup and a PDQ access code or the services of a medical library with online searching capability. Most Cancer Information Service offices (1–800–4–CANCER) provide physicians with free PDQ searches and can tell doctors how to get regular access to the database. Patients may ask their doctor to use PDQ, or they may call 1–800–4–CANCER themselves to request a search. Information specialists at this toll-free number use a variety of sources, including PDQ, to answer questions about cancer prevention, diagnosis, treatment, and research.

Selected References

The materials marked with an * are distributed free of charge by the NCI. Ordering information is provided on page 22. The other items are not available from the NCI; they can be found in medical libraries, many college and university libraries, and some public libraries.

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Additional Information

For more information on this subject and for other National Cancer Institute publications, write to the Office of Cancer Communications, National Cancer Institute, Bethesda, MD 20892, or call the Cancer Information Service toll-free at

1-800-4-CANCER

In Hawaii, on Oahu, call 524-1234 (call collect from neighboring islands). Spanish-speaking CIS staff members are available to callers from the following areas (daytime hours only): California, Florida, Georgia, Illinois, New Jersey (area code 201), New York, and Texas.

This Research Report was written by Lauren E. Dickie and its scientific content has been approved by National Institutes of Health scientists. Please direct questions or comments to the Research Reports Editor, National Cancer Institute, Office of Cancer Communications, Bethesda, MD 20892.